Multi-formalism Modelling of Cardiac Tissue

Antoine Defontaine, Alfredo I. Hernandez, Guy Carrault

Multi-Formalism Modelling of Cardiac Tissue

Antoine Defontaine, Alfredo Hernández, and Guy Carrault

LTSI - INSERM U642,
Université de Rennes 1,
Campus de Beaulieu, Bât 22,
F-35042 Rennes Cedex, France
http://www.ltsi.univ-rennes1.fr

Abstract. Many models of the cardiovascular system (e.g. cardiac electrical activity, autonomous nervous system, ...) have been proposed for the last decades. Research is now focusing on the integration of these different models, in order to study more complicated physiopathological states in clinical applications context. To get round the practical limitations of existing models, multi-formalism modelling appears as a way to ease the integration of these different models together.
This paper presents an original methodology allowing to combine different types of description formalisms. This method has been applied to define a multi-formalism model of cardiac action potential propagation on a 2D grid of endocardial cells, combining cellular automata and a set of cells defined by the Beeler-Reuter model. Results, obtained under physiologic and ischemic conditions, highlight the improvements in term of computing compared with mono-formalism systems, while keeping the necessary explanatory strength for a practical clinical use.

1 Introduction

Cardiac modelling and simulation have been the subject of important research during the last three decades. Different models of the electrical activity have been proposed for the main types of cardiac myocites in normal or pathological conditions [1, 2]. These models are defined at different levels of detail (i.e. taking into account more or less independant ionic currents) and different formalisms (usually ordinary differential equations for cellular defined models and cellular automata for models defined at a wider scale).

Typically, individual models defined at a *same level* of detail and under the *same formalism* are coupled in the form of 1D, 2D or 3D objects to represent a given part of cardiac tissue, or to reproduce the whole cardiac anatomy. Applications range from the understanding of the cardiac function, in normal or pathologic conditions (e.g. ischemia [3]), to the assistance in the definition of new therapies [1]. However, none of the existing approaches allows a complete consideration of whole cardiac activity and, choice and compromise have to be done depending on the expected simulation.

After a short presentation of the main current cardiac modelling approaches, this paper proposes an original modelling and simulation method based on a

generic multi-formalism approach. Relevant results obtained under normal or pathologic (ischemia) conditions, highlighting the interest of the method in terms of computational needs and clinical interpretation, are presented and discussed on the remaining parts.

2 Current views of cardiac modelling problem

Two different approaches can be identified in the definition of computational cardiac models, depending on the level of detail employed for their definition: whole cardiac models at a cellular level and complete heart models developed at the tissue or organ level [4, 5]. Both views still suffer from difficulties that reduce their clinical application: the former approach requires heavy computational resources while the later one is not able to reproduce certain pathologies defined at different scales. A hybrid approach combining the two previous types of description is now emerging.

2.1 Cellular level

A number of cardiac models have been proposed at a cellular level [6, 7, 1]. In this type of approach, systems are defined by a network of many 'atomic' cells whose description is usually implemented by means of models representing different physiological aspects [8–11].

In general, a system of such cells is defined as follows [12, 13, 5]:

$$\frac{dV_i}{dt} = G(P_C) + K \cdot \bigtriangledown^2 V \tag{1}$$

where V_i is the membrane potential of cell i, G is a function that depends on a set of parameters P_C, K is a diffusion coefficient and $\bigtriangledown^2 V$, the Laplacian of the membrane voltages of the neighbouring cells.

Usually, thousands of cells are coupled in a predefined geometry to represent one or more cavities of the heart. Due to this extensive definition, models defined at the cellular level require massive computing resources. Moreover, their coupling with other models remains tricky and even with high performance calculating resources, computational time limits their clinical application.

2.2 Tissue level

Models developed at the tissue level are based on a coupled network of macrostructures, often using a cellular automata (CA) approach, which represent specific anatomical structures of the heart [14–16].

The state behaviour of each automaton of such an event-based approach can be defined by [17, 5]:

$$E = H(P_A) \tag{2}$$

where E is the state of the cellular automaton and H is the function governing internal state transitions, depending on parameters P_A. When a given macrostructure reaches the depolarisation state, neighbouring tissues are activated by the transmission of a flag (external state transition). Particular properties of cardiac cells, such as the dependance of the depolarisation slope to the stimulation frequency, have also been included in some CA models [17].

Due to their low computational costs, this kind of models has been used in different clinical setups. Although some major cardiac rhythms can be reproduced and explained by these models, some difficulties remain when dealing with complex rhythms and when simulating pathologies implying modifications at a cellular or molecular level such as myocardial ischemia [17]. These difficulties are inherent to the definition of the models at a macroscopic scale and, consequently, to the inability of considering a physiopathological process at a cellular level.

2.3 Multi-formalism approach

In this context, one can easily think that a way to take advantage from the benefits of each approach would be to selectively define different regions of the modelled heart at different scale levels, depending on its physiological or pathological state. Such a consideration is also legitimated by the practical clinical diagnosis performed by the physician, which aims at refining progressively the investigated region of the heart, going from a global consideration of healthy parts to a precise analysis of pathological sources.

A similar problem of hybrid approach has been identified in other applications [18] and has led to specific researches and developments on multi-formalism modelling (DEVS++, AToM^3, Modelica, ...). This type of modelling consists in gathering components described in different ways (known as description formalisms), which can be basically summarised as discrete or continuous specifications. Although these approaches reveal efficient in traditional engineering fields, few works have been done on specific modelling of natural processes, including cardiac modelling.

This approach parallels recent works by Poole *et al* [19] which presented preliminary results of a multi-formalism approach on 1D segments of cardiac tissue, rather than an exhaustive use of supercalculation. They expanded the general theory of synchronous concurent algorithms (SCA) which consists in unifying the different types of models on a global clock measuring discrete time. Indeed, the advantage of a multi-formalism method lies in the partial use of discrete models (cellular automata) that require less computational resources than corresponding continuous models (based on ODE definition). Nevertheless, Poole's work suffer from certain limitations: i) their use of SCA can be considered as a cosimulation approach [18] limiting the gains in term of computing time, ii) the way the different models are coupled is unclear and iii) used cellular automata lack of dynamical properties.

3 Proposed methodology

The proposed approach tries to go deeper in the way of dealing with a multi-formalism definition. Based on Zeigler's work [20], our main goal has been to define a tool as generic as possible with ease of use in other fields than cardiology and ease of implementing new types of models or new simulation algorithms. The main difficulty associated with such a multi-formalism approach concerns the definition of a unique but generalisable coupling criteria, particularly at the interfaces between atomic models of different formalisms. Moreover, the proposition of such a method should be accompanied by a quantitative method to evaluate the differences between the multi-formalism approach and a monoformalism used as gold standard.

In our work, we have chosen to use a coupling function of the neighbouring potential as performed for continuous models [5]. In our concern for developing as generic as possible a system, using the same manner of coupling (same method in the tissue model) for all the types of tissues allows to define a unique standard coupling procedure. Adaptations of the methods will be done in each model definition as follows:

Let $C^{F_.}_{i,j,k}$ be an atomic cell component of a cardiac tissue, defined by a formalism $F_.$ (where $F_.$ can be continuous F_c or discrete F_d). The generic coupling behaviour can be extended from (1) as follows:

$$C^{F_.}_{i,j,k} = G_{F_.}(P) + Coup_{F_.}(K \cdot \bigtriangledown^2 V) \tag{3}$$

where $G_{F_.}$ is the function of parameters P, $Coup_{F_.}$ the coupling method and K as defined in (1). The coupling method can be defined as follows:

$$Coup_{F_.} = \begin{cases} thres & \text{if the cell model is discrete}(F_. = F_d) \\ id & \text{if the cell model is continuous}(F_. = F_c) \end{cases} \tag{4}$$

where *id* is the identity function and *thres* a threshold function setting external activation for the cellular automata if the input is greater than the limit value necessary for depolarisation of an equivalent continuous model (Fig. 1).

With this approach, the coupling between a set of cells of a tissue will always be defined by the generic definition (3), whatever their description formalisms are. This allows to keep into account the influence of the neighbouring cells during the whole activation. Consequently, a minimum of information will be lost during the propagation of depolarisation fronts, allowing not to alter the clinical interpretation. Each specification of the methods will be done for each model definition, in the sense of an object oriented approach.

4 Implementation considerations

Traditional processing of the 'cable equation' (1) is usually done using a centralised approach (Fig. 3(a)) where the whole simulation is done at the same level and, usually, inside a unique simulation loop which can solve only one modelling

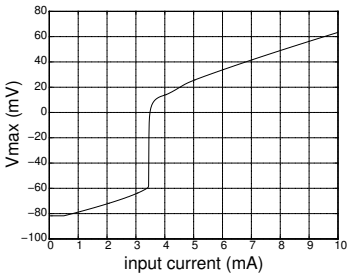

Fig. 1. Peak membrane voltages for a Beeler-Reuter model, as a function of a variable input current. The value retained for the activation threshold of cellular automata is $3.5\ mA$.

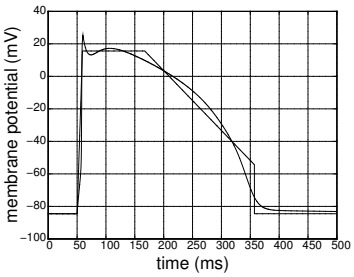

Fig. 2. Output of the proposed CA model, representing a piece-wise linear fitting of the BR action potential.

formalism. An alternative to this approach, which is particularly adapted to the multi-formalism case, has been proposed by Zeigler [20]. It is based on a distributed simulator structure that parallels the model architecture (Fig. 3(b)). The introduction of coordinator objects grouping different sub-models, eases the use of a multi-formalism approach and can facilitate a parallel implementation of the simulator.

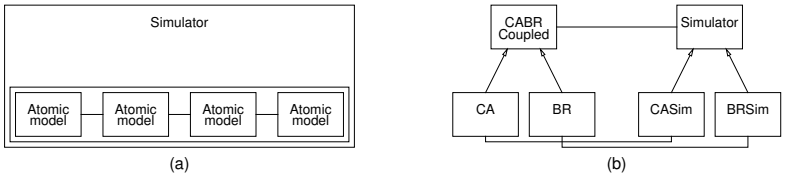

Fig. 3. Simulation approaches: a. classical mono-formalism centralised approach: the link between the different components and the whole simulation are done in a unique level; b. distributed multi-formalism approach: the coupled model represents the coordinator with an associated simulator.

We have developed a generic library of modelling and simulation based on this architecture. It consists of a list of different types of models inherited from a standard mother class. By this definition, inherited classes can represent any combination of elements (atomic element, structure of atomic elements, complex structure mixing atomic elements and pre-existing structures, ...). Based on Zeigler's introduction of coordinator objects, simulation is done deepening the level of the considered structure up to reaching only atomics elements and

specific simulators, adapted to each atomic model's formalism, are used. The simulation of the global system is performed at the coordinator level whereas each component is simulated at the model level.

5 Results

5.1 Experimental settings

The proposed generic method has been implemented on a *256* x *256* square tissue of endocardial cells, corresponding to an average size of *10 mm* x *10 mm*. The coupling coefficient K has been set in order to maintain a conduction velocity of $0.5\ m.s^{-1}$ in the case of healthy tissues.

Different types of tissues have been simulated: mono-formalism healthy (discrete or continuous), multi-formalism healthy (discrete and continuous), mono-formalism ischemic and multi-formalism ischemic. In the case of multi-formalism tissues, peripheral cells are defined by a discrete approach while the *64* x *64* central cells are continuous.

Cellular models fall in the two previous categories:

- Continuous models: Beeler Reuter (BR) model [9] is used in the case of healthy tissues. Ischemic model used has been adapted from the Beeler Reuter model by Sahakian [21] to take into account membrane current modifications. A different coupling coefficient is also used with gradual transition from normal to pathologic cells [21, 3, 13].
- Discrete models: Cellular automata (CA) traditionally used are composed of main action potential states (i) idle, ii) rapid depolarisation, iii) absolute refractive period and iv) relative refractive period) but suffer from a lack of dynamical properties. Contrary to those static models, our automata possess two main dynamical properties: refractory period dependance to the stimulation frequency as well as the response to premature activations [17]. The CA output is defined by means of a piece-wise linear function fitting the Beeler Reuter action potential, where each linear segment is associated to a different state of the CA (Fig. 2).

5.2 Simulation results

Depolarisation fronts obtained for healthy tissues are presented in Fig. 4(a-c). The differences between BR defined mono-formalism tissue and the two others are quantified in Fig. 4(d-e).

Depolarisation fronts are coherent with the known behaviour of electrical propagation on cardiac tissue. Slight differences that appear between BR tissue and the two others (Fig. 4(d-e)) are due to the atomic behaviour of each model and, especially, to the difference on the depolarisation slopes (Fig. 2). Even if the previous results are interesting only for validation purposes, it is important to note that the clinical interpretation won't be altered, from a qualitative point of view, for discrete or hybrid tissues, presenting the same mean propagation

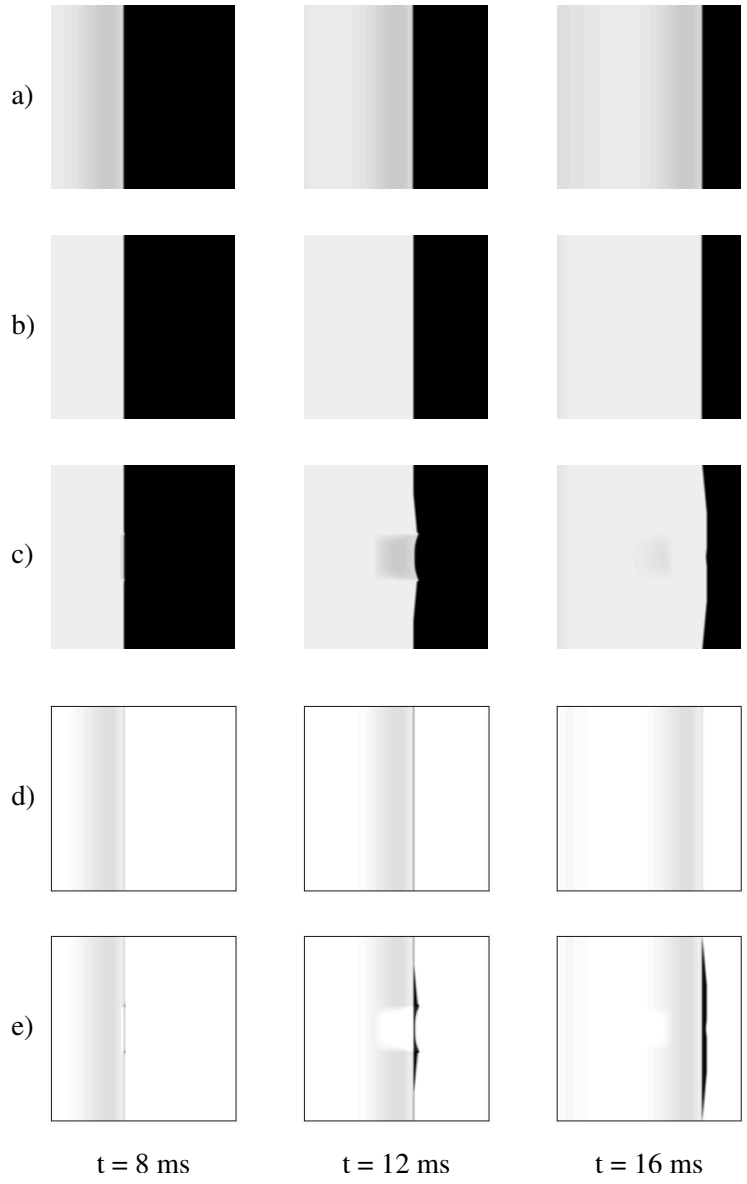

Fig. 4. Depolarisation fronts for healthy tissues: a. BR tissue, b. CA tissue, c. CABR tissue. Greyscale ranges from black for resting potential ($-84.5\ mV$) to white for a depolarised potential ($22\ mV$).
Differences in the depolarisation fronts for healthy tissues: a. between BR and CA, b. between BR and CABR. Greyscale ranges from white where no difference appears to black for the greatest differences.

properties (i.e. conduction velocities). Moreover, experimental results show a reduction of the computing time in the case of multi-formalism approach compared to mono-formalism one, highlighting the clinical interest of such a method.

Such a multi-formalism approach takes sense when dealing with ischemic tissues. Results obtained for ischemic tissues are presented in Fig. 5(a-b) and the difference between mono and multi-formalism simulation are quantified in Fig. 5(c).

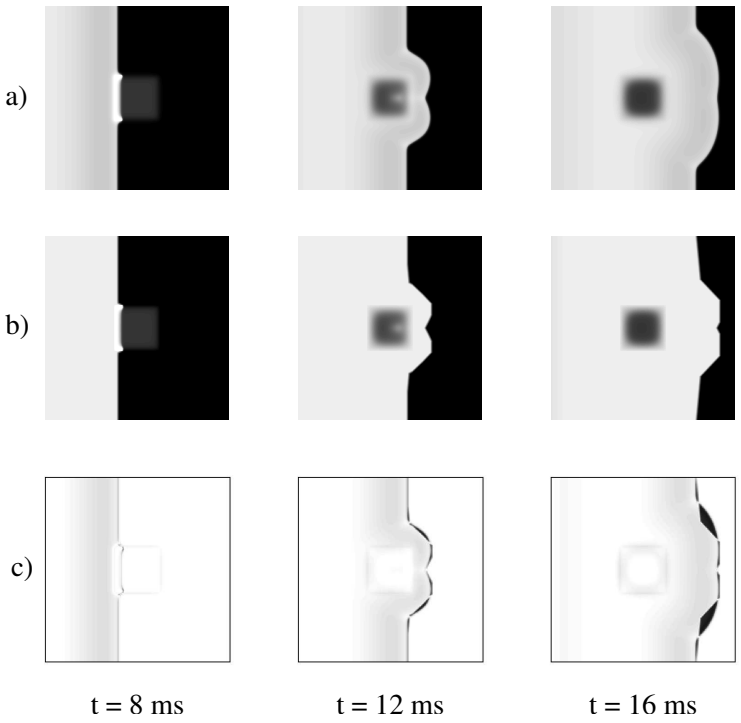

Fig. 5. Depolarisation fronts for ischemic tissues: a. BRIsch tissue, b. CAIsch tissue. c. Differences in the depolarisation fronts for ischemic tissues.

Even if the spatial depolarisation fronts simulated by these two apporaches are not strictly identical, similar behaviour can be observed in both tissues:

- Alteration of the propagation front linked with the presence of ischemic area.
- Abnormal and incomplete depolarisation of pathologic cells (note the small difference in the *64* x *64* centre square of Fig. 5(c)): i) quicker depolarisation in the border of the ischemia, ii) depolarisation block at the center of the ischemic area, iii) modification of the depolarisation front in the shadow of the ischemia.

– Temporal correspondance of the simulated events.

These experimental results have brought out improvements in terms of computing time compared with mono-formalism systems, while keeping the necessary qualitative explanatory strength for a practical clinical use.

6 Conclusion and perspectives

An original simulation method based on a multi-formalism approach has been presented in this paper. Depolarisation fronts obtained from healthy or ischemic tissues have highlighted that the qualitative clinical interpretations are not altered despite the partial use of simpler description models (CA). Experiments have also shown a reduction of the computing time that would ease a practical use of such models.

One great advantage of this method is the possibility of simulating physiopathological states even in a hybrid approach. Compared to other projects in the same field [19], which use Aliev-Panfilov model (a morphological description of the action potential), the proposed method lets us integrate physiologically detailed models, such as the BR model, while still minimizing the global computing expenses.

Current development consist in improvements of our simulation library: i) integration of more detailled models such as Luo and Rudy [10, 11] and ii) improvement of our CA simulation method, by taking into account their specific state transition properties. Future work will deal with the extension of these results to a 3D cardiac volume obtained from current developments in our laboratory [22]. It will be based on a multi-scale description of the volume combined with the presented multi-formalism approach, with the constant aim of not altering the clinical interpretations by being able to reproduce the important physiological markers of cardiac electrical activity.

Acknowledgements

This work has been partly supported by the ECOS-NORD cooperation program, action number V03S03.

References

1. Noble, D.: Modeling the heart – from genes to cells to the whole organ. Science. **295** (2003) 1678–1682
2. Bardou, A.L., Auger, P.M., Birkui, P.J. and Chasse, J.L.: Modeling of cardiac electrophysiological mechanisms: from action potential genesis to its propagation in myocardium. Critical Review of Biomedical Engineering. **24** (1996) 141–221
3. Wilders, R., Verheijck, E.E., Joyner, R.W., Golod, D.A., Kumar, R., van Ginneken, A.C.G., Bouman, L.N. and Jongsma H.J.: Effects of Ischemia on Discontinuous Action Potential Conduction in Hybrid Pairs of Ventricular Cells. Circulation. **99** (1999) 1623–1629

4. Trudel, M.-C., Dubé, B., Potse, M., Gulrajani, R.M. and Leon, L.J.: Simulation of QRST Integral Maps With a Membrane-Based Computer Heart Model Employing Parallel Processing. IEEE Transactions on Biomedical Engineering. **51** (2004) 1319–1329
5. Defontaine, A., Hernández, A. and Carrault, G.: Modelling and Simulation: Application to Cardiac Modelling. Acta Biotheoretica. **52** (2004) 273–290
6. Porman, J.B.: A Modular Simulation System for the Bidomain Equations. Department of Electrical and Computer Engineering, Duke University. (1999)
7. McCulloch, A. Bassingthwaighte, J., Hunter, P. and Noble, D.: Computational bilogy of the heart: from structure to function. Progess in Biophysics and Molecular Biology. **69** (1998) 153–155
8. Aliev, R.R. and Panfilov, A.V.: A Simple Two-variable Model of Cardiac Excitation. Chaos, Solitons and fractals. **7** (1996) 293–301
9. Beeler, G.W. and Reuter, H.: Reconstruction of the action potential of ventricular myocardial fibres. Journal Of Physiology. **268** (1977) 177–210
10. Luo, C.H. and Rudy, Y.: A model of the ventricular cardiac action potential. Depolarization, repolarization, and their interaction. Circulation Research. **68** (1991) 1501–1526
11. Luo, C.H. and Rudy, Y.: A dynamic model of the cardiac ventricular action potential (I & II). Circulation Research. **74** (1994) 1071–1113
12. Keener, J. and Sneyd, J.: Mathematical Physiology. Springer-Verlag. (1998)
13. Clayton, R.H., Parkinson, K. and Holden, A.V.: Re-entry in computational models of ischaemic myocardium. Chaos, Solitons and Fractals. **13** (2002) 1671–1683
14. Malik, M., Cochrane, T., Davies, D.W. and Camm, A.J.: Clinically relevant computer model of cardiac rhythm and pacemaker/heart interaction. Medical and Biological Engineering and Computing. **25** (1987) 504–512
15. Ahlfeldt, H., Tanaka, H., Nygards, M.E., Furukawa, T. and Wigertz, O.: Computer simulation of cardiac pacing. Pacing Clinical Electrophysiology. **11** (1988) 174–184
16. Virag, N., Vesin, J.M. and Kappenberger, L.: A computer model of cardiac electrical activity for the simulation of arrhythmias. Pacing Clinical Electrophysiology. **21** (1998) 2366–2371
17. Hernández, A.I., Carrault, G. and Mora, F.: Model-based interpretation of cardiac beats by evolutionary algorithms: signal and model interaction. Artificial Intelligence in Medicine. **26** (2002) 211–235
18. de Lara, J. and Vangheluwe, H.: Computer aided multi-paradigm modelling to process petri-nets and statecharts. In International Conference on Graph Transformations (ICGT), Lecture Notes in Computer Science. **2505** (2002) 239–253
19. Poole, M.J., Holden, A.V. and Tucker, J.V.: Hierarchical reconstructions of cardiac tissue. Chaos, Solitons and Fractals. **13** (2002) 1581–1612
20. Zeigler, B.P., Praehofer, H. and Kim, T.G.: Theory of Modeling and Simulation, Second Edition, Integrating Discrete Event and Continuous Complex Dynamic Systems. Academic Press. (2000)
21. Sahakian, A.V., Myers, G.A. and Maglaveras, N.: Unideirectional Block in Cardiac Fibers: Effects of Discontinuities in Coupling Resistance and Spatial Changes in Resting Membrane Potential in a Computer Simulation Study. IEEE Transactions on Biomedical Engineering. **39** (1992) 510–522
22. Garreau, M., Simon, A., Boulmier, D. and Guillaume H.: Cardiac Motion Extraction in Multislice Computed Tomography by using a 3D Hierarchical Surface Matching process. IEEE Computers in Cardiology Conference, Chicago, USA. (2004)